

REMARKS

Claims 1-10, 15 and 20-22 were pending. Claims 58-70 have been added. Claims 58-70 are supported by the specification and claims as originally filed, including by original claim 20.

Claims 1, 10, 15, 20 and 22 have been amended.

Claim 1 is amended to recite that the parent has more than 50% homology with the amino acid sequence shown in SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:5. Support for this amendment is found in the specification and claims as originally filed, including by original claim 20. Claim 1 is also amended to reference Appendix 1.

Claim 10 is amended to recite that the parent has more than 50% homology with the amino acid sequence shown in SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:5. Support for this amendment is found in original claim 20. Claim 10 is also amended to recite the step of modeling the parent pullulanse on the three-dimensional structure of SEQ ID NO:1 depicted in Appendix 1. Claim 10 is also amended to relocate the subject matter of "optional" step c) to new dependent claim 70.

Claim 15 is amended to specifically recite the limitation found in claim 4, namely, that the increased thermostability is defined by "differential scanning calorimetry."

Claim 22 is amended to relocate the subject matter of "optional" step d) to new independent claim 57.

The specification has been amended to comply with the sequence rules set forth in 37 C.F.R. 1.82 by including appropriate sequence listing numbers. A paper copy of the sequence listing is submitted herewith. The computer-readable form in this application is identical with that filed in application no. 09/514,599 filed February 28, 2000. In accordance with 37 CFR 1.821(e), please use the last computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. The content of the attached Sequence Listing and of the computer readable form filed in the parent application is the same. No new matter is added.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Election/Restrictions

Claims 1-10, 15 and 20-22 were subject to both a restriction requirement and an election of species requirement. It is alleged that the claims encompass two separate inventions, namely, Group I (claims 1-9, 20 and 21) drawn to a method for producing a variant of a parent pullulanase via nucleic acid modification and Group II (claim 10, 15 and 22) drawn to a method of producing a variant of a parent pullulanase via protein modeling. The claims were also subject to a species election, requiring Applicants to elect one of the following species:

- a) increased isoamylase activity (claim 3);
- b) improved thermostability, determined by
 - i. differential scanning calorimetry (claim 4);
 - ii. T1/2 assay for liquefaction (claim 5);
 - iii. assay for residual activity after liquefaction (claim 6)
 - iv. T1/2 assay for saccharification (claims 7-9).

Group I and species a) were elected with traverse.

The restriction requirement is clearly not proper. Both of the alleged separate inventions claim methods for constructing variant pullulanases using modeling. Applicants respectfully submit that whether the variant is constructed via a nucleic acid modification or via an amino acid substitution is clearly not indicative of separate inventions in the present case. In this regard, a modification via an amino acid substitution can clearly encompass a modification via a nucleic acid modification, and indeed, such manner, would be a preferred method for making an amino acid change.

Moreover, the Examiner's own statement of the appropriate class and subclass to be searched is also clear evidence that the restriction requirement is improper. Indeed, the Examiner's stated area of search for both the inventions is identical, namely, class 702, subclass 72, which clearly reveals that there would be no additional burden on the Examiner to search all of the pending claims.

Notwithstanding the above arguments, as amended, claims 1 and 10 are even more closely related, including an identical modeling step (step a), thereby rendering the restriction requirement moot.

Applicants also respectfully submit that the species election requirement is also improper. Species a) and b) merely recite two separate properties which can be improved by the claimed methods. There is clearly no burden on the Examiner to search both properties, as the exact same art will be involved in such evaluation.

Applicants respectfully request reconsideration and withdrawal of the restriction and species requirements.

II. The Rejection of Claims 1-3, 20 and 21 under 35 U.S.C. 112

Claims 1-3, 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim 1 and its dependent claims are rejected as indefinite for the allegation that step (b) requires an alteration in the structure of the parent pullulanase, while the modification of the nucleic acid in step (c) does not appear to be drawn to this alteration.

This rejection is respectfully traversed. Step b) recites "identifying in the three-dimensional structure obtained in step (a) at least one structural part of the parent pullulanase, wherein an alteration in said structural part is predicted to result in an altered property." Step c) then recites "modifying the nucleic acid sequence encoding the parent pullulanase to produce a nucleic acid sequence encoding a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said structural part."

Accordingly, the modification in step c) is clearly drawn to the structural part identified in step b). Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 1 and its dependent claims are also rejected as indefinite for the allegation that it is unclear whether the phrase "three-dimensional structure of SEQ ID NO:1" is intended to mean the fold structure of the nucleic acid or the three-dimensional of its encoded protein."

As amended, claim 1 now references "the three-dimensional structure of SEQ ID NO:1 depicted in Appendix 1." Appendix 1 is a list of the atomic coordinates for the three-dimensional structure of the encoded protein. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 1-3, 20 and 21 under 35 U.S.C. 112

Claims 1-3, 20 and 21 are rejected under 35 U.S.C. 112, as allegedly lacking enablement.

The Examiner states:

Although the prior art as well as the specification provides for a method of modeling a parent pullulanase on a three-dimensional structure of the protein (i.e., amino acid sequence), it would require an undue amount of experimentation to practice the claimed method which requires a skilled artisan to model a three-dimensional structure of a parent pullulanase based on a nucleic acid sequence of a template protein because neither the prior art nor the specification provides any guidance for such a method.

As amended, the claims recite that that parent pullulanase has more than 50% homology with the amino acid sequenced shown in SEQ ID NO:1, SEQ NO:3 or SEQ ID NO:5. Claim 20 and claims 58-63 recite additional preferred embodiments, in which the parent pullulanase is more than 60%, 70%, 80%, 90%, 95% and 99% homologous to SEQ ID NO:1, SEQ NO:3 or SEQ ID NO:5. (Claims 10, the only other independent claim, also recites that the parent pullulanase has more than 50% homology to SEQ ID NO:1, SEQ NO:3 or SEQ ID NO:5.)

Applicants respectfully submit that an artisan, once apprised of Applicants' invention, and using computer modeling programs available in the art at the time of the invention (such as, e.g., Homology 95.0, available from Biosym, the User Guide Table of Contents of which is attached hereto as Exhibit A), could readily create accurate three-dimensional structures of parent pullulanase which are more than 50% homology to SEQ ID NO:1, 3 or 5, including more than 60%, 70%, 80%, 90%, 95% and 99% homology to SEQ ID NO:1, SEQ NO:3 or SEQ ID NO:5. Once apprised of Applicants' invention, an artisan could then also use such generated three-dimensional structures to prepare variant pullulanases. See, e.g., Johnathan Greer, "Comparative Modeling Methods: Applications to the Family of the Mammalian Serine Proteases," Proteins: Structure, Function, and Genetics 7:317-334 (1990); Johnathan Greer, "Protein Structure and Function by Comparative Model Building," Annals of the New York Academy of Sciences, , Vol. 439, 44-63 (1985) (attached hereto as Exhibits B and C, respectively).


Accordingly, Applicants submit that one skilled in the art is enabled to carry out the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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